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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
05/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47,112 and 113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response to the notice of non-compliant amendment filed on 1/29/07 has been entered. The applicant statement that this response is identical in substance to the response filed on 9/17/06 is acknowledged. Claims 3, 8-29, 32-37, 40, 46, and 48-111 are canceled. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 are pending and currently under examination. An action on the merits follows.

It is again noted for the record that although claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 still read broadly on any non-human transgenic animal, the claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse. It is further noted that the species of mouse was elected **without** traverse, and neither the elected species nor the generic claims are found to be allowable.

Claim Rejections - 35 USC § 103

The rejection of claim 112 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, is withdrawn in view of the amendment to claim 112 which adds the limitation the transgenic non-human mammal comprises unrearranged human T cell receptor alpha and beta loci.

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that none of the cited references provide the requisite teaching of a mouse comprising human TCR loci that are capable of undergoing productive rearrangement. Specifically, the applicant argues that there are notable differences between developmental regulation of the assembly of αβ TCR and γδ TCR based on notable differences in regulatory and signal elements in each loci, cell type dependence and developmental timing, citing Godfrey et al., and Lauzurica and Krangel provided as in appendices A and B filed with the previous response. The applicant also cites Sleckman et al. as teaching other notable differences in regulation of αβ TCR and γδ TCR loci, however despite the statement that a copy of this reference was provided with the response, no such copy was received by the office. As such, the teachings of Sleckman et al. cannot be evaluated. Based on these putative differences between the α and β TCR loci and the δ TCR loci, the applicant concludes that the teachings of McMurry et al. in particular do not provide a reasonable expectation of success in achieving productive rearrangement of α and β TCR loci in transgenic mice as claimed.

In response to the references cites by applicants, the Lauzurica and Krangel article is an earlier article by some of the authors of McMurry et al. and simply details the importance of loci

specific enhancer elements in regulating TCR loci rearrangement and further teaches that elements of the recombination machinery necessary to carry out rearrangement are expressed in a cell specific and developmentally regulated fashion. Godfrey et al. provides guidance as to the various stages of T cell development, including the order of TCR loci rearrangement. Neither of these references provides any evidence or suggestion that a human TCR loci in the genome of a transgenic mouse would not be capable of productive V(D)JC rearrangement. Instead, these references simply teach that each loci contains its own specific regulatory elements, and that rearrangement of the loci takes place in T cells during regulated stages of T cell development. McMurry et al. constructed the transgenic mouse comprising the human TCR δ locus such that the human loci would be present in T cells such that the human sequences would be exposed to the proper signals and machinery to initiate and allow VJC rearrangement during normal development. Further, the human TCR δ locus utilized by McMurry et al. contained all the appropriate human δ specific regulatory elements necessary for successful VJC rearrangement as evidenced by the fact that VJC rearrangement of the human TCR δ locus was in fact observed by McMurry et al. Further, Rack et al. and Rowen et al. provide teachings for vectors comprising unrearranged human TCR alpha and beta loci which comprise the regulatory elements and enhancers which McMurry et al. demonstrate are essential to proper V(D)JC rearrangement during T cell development.

In addition, applicant's argument that the complexity of the TCR loci and the complexity of the developmental regulation of rearrangement of the αβ TCR and γδ TCR loci would preclude a reasonable expectation to success in achieving productive rearrangement with human α or β TCR loci is not agreed. McMurry et al. teaches that the TCR and Ig (immunoglobulin)

loci are similar in structure and that rearrangement of the TCR and Ig loci utilizes the same recombination machinery. Like TCR β loci resembles the Ig heavy chain loci in that both comprise numerous V region genes, including pseudogenes, D region genes, J region genes, and C region genes, and the TCR α loci resembles the Ig light chain kappa loci in that both comprises numerous V region genes, including pseudogenes, J region genes, and a C region gene. Furthermore, the prior art of record, WO 98/24893 and US. Patent 6,150,584, both cited by applicants in IDS submissions, provides clear evidence of the production of transgenic mice with deletions in the endogenous immunoglobulin heavy and kappa light chain loci and comprising unrearranged transgenes comprising the human heavy chain and kappa light chain immunoglobulin loci which are fully capable of productive rearrangement of the transgenes resulting in the expression of functional antibodies. As such, the teachings of McMurry et al. regarding the similarities between the Ig and TCR loci and the state of the art of transgenic mice comprising unrearranged heavy and light chain loci would have led the skilled artisan to have a reasonable expectation of success that the presence of unrearranged TCR α or β TCR loci in transgenic mice would lead to productive rearrangement and expression of functional αβ TCR in T cells.

Finally, it is noted that the applicant has primarily presented arguments against McMurry et al. While these arguments have been addressed above, please note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection is based on the combined teachings of Littman et al. in view of Mombaerts et al., McMurry et al.,

Rowen et la., and Rack et al. of record. Therefore, for reasons of record and the discussion above, the rejection stands.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER